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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,032	11/03/2003	Hani Sabbah	1059.00096	3424

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EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1657	
MAIL DATE	**DELIVERY MODE**
07/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,032	SABBAH ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/24/2008 has been entered.

Claims 2 and 15 as amended 4/24/2008 are pending and under examination.

Claim Rejections - 35 USC § 112

Indefinite

Claims 2 and 15 as amended are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite for being incomplete because it does not clearly point out what are active steps of the claimed method. It is unclear as claimed what and how many active steps are included in the claimed method. Is “and improving cardiac function” after administering is an active step? Further, it is unclear what is intended as evaluation protocol in the step of “improving cardiac function”.

Claim 2 recites the limitation "the products" for administering. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2 and 15 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over US 7,097,832 (Kornowski et al), Hamano et al. (Cell Transplantation. 2000, Vol. 9, pages 439-443) and US 6,368,636 (McIntosh et al.).

Claims are directed to a method of improving cardiac function by administering hypoxic bone marrow stem cell (BMSC) preconditioned medium wherein the hypoxic BMSC preconditioned medium is produced at 95% nitrogen/5% carbon dioxide. Some claims are further drawn to mode of administering such as directly to heart, intravenously or intracoronary.

The cited reference US 7,097,832 (Kornowski et al) as a whole teaches and/or suggest a method of improving cardiac function, treating ischemic myocardium and enhancing blood vessel formation in ischemic tissue including heart by administering a "conditioned" medium comprising bone marrow derived cells and the bone marrow cell secretion products that provide for angiogenesis (entire document and, in particular, col. 18, lines 50-55; col. 17, lines 7-15; col. 15, lines 56-60). The therapeutic "conditioned" medium is obtained under conditions that stimulate production of angiogenic factors including VEGF and HIF-1 by the bone marrow derived cell populations (col. 16, lines 44-58). The cited patent US 7,097,832 (Kornowski et al) teaches that the optimization strategies for stimulation of angiogenic factor production prior to administration include an *ex vivo* exposure of bone marrow cells to hypoxia (col. 16, lines 45-

46). Thus, the teaching of the cited patent US 7,097,832 (Kornowski et al) as a whole provides for the same concept of improving cardiac function by administration of a therapeutic preconditioned medium of bone marrow cells and their secreted factors/products wherein the preconditioned medium is made *ex-vivo* under hypoxic culturing conditions prior to administration.

In addition, the reference by Hamano et al. is relied for the teaching that culturing bone marrow cells under hypoxic conditions enhances production of angiogenic factors such as VEGF in the culture supernatants relatively to normoxic conditions (entire document including abstract and table 1). The exemplified hypoxic conditions allow for the presence of some 2% of oxygen in the gas mixture (page 440, col.1, par. 3) but the cited reference clearly demonstrates that prolonged exposure of *in vitro* cultures to hypoxic conditions, when oxygen would be exhausted, further increases or accelerates production of angiogenic factors in supernatants (table 1). The claimed limitation drawn to the use of a gas mixture comprising 5% carbon dioxide and 95% nitrogen for making a therapeutic product is a product-by-process type limitation wherein the claims are not limited to the manipulations of recited steps but they are rather limited to the final structure of the product obtained. It is well within the purview of ordinary skill practitioner to use nitrogen as a balance gas to flush out oxygen from cultivation chamber to provide for hypoxic culturing conditions.

Furthermore, it is well known that bone marrow cell populations contain various stem cells including mesenchymal stem cells (MSC) and that MSC can be isolated, expanded in culture and used as source of MSC supernatant (US 6,368,636 at col. 9, lines 54-55 and col.6, lines 5-6). The cited US 6,368,636 is also relied upon for the teaching of additional beneficial

effects of the bone marrow MSC supernatants (col. 6, lines 1-10) such as reduction of transplant rejection including heart transplants (col. 5, line 38; col. 28, lines 1-10).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to administer hypoxia-preconditioned culture medium comprising bone marrow derived cells and the bone marrow cell secretion products to the ischemic heart with a reasonable expectation of success in improving cardiac function as taught and/or suggested by US 7,097,832 because hypoxic culture conditions enhances production of angiogenic factors by bone marrow cell populations as taught by US 7,097,832 and as clearly demonstrated by Hamano et al.

One of skill in the art would have been motivated to administer the bone marrow stem cell secretions for the benefits in promoting new blood vessel growth and restoring function of ischemic heart as taught and/or suggested by US 7,097,832. One of skill in the art would have been motivated to administer the bone marrow mesenchymal stem cell supernatants to reduce immune response during heart transplantation as suggested by US 6,368,636, thereby, improving cardiac function within the broadest meaning of the instant claims.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 4/24/2008 have been fully considered but they are not found persuasive.

With regard to the claim rejection under 35 U.S.C. 103(a) as being unpatentable over US 7,097,832 (Kornowski et al) applicants argue that the cited patent discloses a method for treating cardiac or myocardiac conditions by administering autologous marrow cells that would secrete therapeutic angiogenic factors at the site of implantation under *in vivo* hypoxic conditions upon administration (response page 7, par. 2). This argument is not found persuasive because the cited US 7,097,832 clearly teaches optimization strategies for conditioning the bone marrow cell therapeutic product prior to injection or prior to administration and the optimization protocol is *ex vivo* exposure of bone marrow cell population to hypoxia (col.16, lines 44-52).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

July 3, 2008

VERA AFREMOVA

PRIMARY EXAMINER

/Vera Afremova/
Primary Examiner, Art Unit 1657